

AWARD NUMBER: W81XWH-15-1-0379

TITLE: Comprehensive genetic characterization of intraprostatic chronic inflammation and prostate cancer in African American men

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REPORT DATE: September 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE September 2017		2. REPORT TYPE Annual		3. DATES COVERED 1 Sep 2016 – 31 Aug 2017	
4. TITLE AND SUBTITLE Comprehensive Genetic Characterization of Intraprostatic Chronic Inflammation and Prostate Cancer in African American Men				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-1-0379	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Elisa Marie Ledet, PhD E-Mail: eledet@tulane.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Tulane University 1430 Tulane Ave, SL-68 New Orleans, 70112				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT African-Americans (AA) have a higher incidence of prostate cancer (PCa) and higher mortality. Stromal and epithelial inflammatory processes have a fundamental role in carcinogenesis and may predict PCa clinical progression. Discovery of novel variants as well as re-discovery of known variants deliver new opportunities for therapeutic advances such as new drug targets and personalized therapy. We hypothesize next-generation whole genome sequencing, paired with new methodologies of intratumoral phylogenetic analyses, will yield pivotal information in elucidating the key genes involved evolution of PCa from precursor inflammatory lesions in AA men. During this research period, extensive translational research training has been completed including both clinical training as well as training in bioinformatics. The most significant outcome of the present study has been the assemblage of a robust database of clinical annotation and follow-up for early stage prostate cancer patients treated at Tulane University Medical Center. This database combined with both clinical and experimental genetic data produced by this study may empower patients and doctors to make personalized treatment decisions and ultimately improve treatment outcomes. Similarly, as product of training, research database and ongoing genetic analyses, the PI has had the opportunity to collaborate on numerous publications, conference presentations, and grant opportunities.					
15. SUBJECT TERMS prostate cancer, African-American, chronic inflammation, next-generation sequencing, translational research, genetics, disparity					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	17	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4
4. Impact.....	7
5. Changes/Problems.....	8
6. Products.....	9
7. Participants & Other Collaborating Organizations.....	12
8. Special Reporting Requirements.....	13
9. Appendices.....	13

1. **INTRODUCTION:** African-Americans (AA) have a higher incidence of prostate cancer (PCa) and higher mortality. Stromal and epithelial inflammatory processes have a fundamental role in carcinogenesis and may predict PCa clinical progression. Prostate inflammation is present in a higher proportion of AA men. Comprehensive identification of the very early genetic alterations associated with progression from inflammation to PCa remains elusive. Understanding and identifying the very early genetic events driving chronic inflammation and development of PCa in AA men may provide insight into disease disparity and clinically actionable opportunities to improve treatment of chronic inflammation, PCa prevention, early detection of high risk PCa, and identification of genes and pathways which may influence PCa recurrence and metastasis. Discovery of novel variants as well as re-discovery of known variants deliver new opportunities for therapeutic advances such as new drug targets and personalized therapy. We hypothesize next-generation whole genome sequencing, paired with new methodologies of intratumoral phylogenetic analyses, will yield pivotal information in elucidating the key genes involved evolution of PCa from precursor inflammatory lesions in AA men.
2. **KEYWORDS:** prostate cancer, African-American, chronic inflammation, next-generation sequencing, translational research, genetics, disparity
3. **ACCOMPLISHMENTS:**
 - **What were the major goals of the project?**
 - Specific Aim 1&2: To independently characterize intraprostatic somatic mutations in prostate tissue derived from tumor and chronic inflammation.
 - Major Task 1: Obtain prostate tissue samples. 100% complete.
 - Major Task 2: Whole-exome sequencing of prostate tissue derived from tumor and chronic inflammation, and germline DNA. 50% complete.
 - Major Task 3: Perform genetic analyses characterizing somatic mutations in prostate tissue samples. 15% completed.
 - Specific Aim 3: To compare and phylogenetically model intraprostatic genetic changes between prostate tissue with chronic inflammation and PCa.
 - Major Task 1: Compare and contrast genetic changes between prostate tissue with chronic inflammation and PCa. 10% complete.

- Major Task 2: Confirm significant genetic alterations in an independent validation cohort. 25% completed.
- **What was accomplished under these goals?**
 - Specific Aim 1&2: To independently characterize intraprostatic somatic mutations in prostate tissue derived from tumor and chronic inflammation.
 - Major Task 1: Obtain prostate tissue samples. 100% complete. A total of 113 patient samples were clinically annotated and screened for inclusion in this study. 52 African American patients with evidence of both chronic inflammation and PCa were identified. 20 patient samples were submitted for review by a pathologist and for tissue preparation. Statistical analyses were performed to assess any significant clinical differences between and within both the African American and Caucasian patient cohorts.

The study sample consisted of 61 African American (AA) and 52 Caucasian (CA) PCa patients who underwent radical prostatectomies (RP) at Tulane Hospital between 2013 and 2015. The presence or absence of chronic inflammation (CI) was determined based on reviews of RP pathology reports from multiple pathologists. Other clinical data was extracted from both biopsy and RP pathology reports. The study examined the relationship between CI, race, percent of positive cores, extraprostatic extension, PSA, PSA density, urinary PCA3 and TMPRSS2, and prostate size (g). Pearson's chisquare, Fisher's exact, and KruskalWallis tests were used to analyze categorical, noncontinuous data; ANOVA tests were used to analyze continuous data. Differences between biopsy and surgical/pathologic Gleason scores and clinical/pathological stages were also assessed. 94 patients (52 AAs and 42 CAs) had CI to some degree and 19 did not (9 AAs and 10 CAs). There was no difference in rate of CI between AA and CA patients ($P = 0.526$). Among all patients sampled, AAs had higher percentages of positive cores ($P = 0.005$), PCA3 copy levels ($P = 0.004$), and PCA3 scores ($P < 0.001$), lower TMPRSS2 scores ($P = 0.039$), and were more likely to have "high" or "intermediate" NCCN risk strata ($P = 0.010$). Among patients with CI, AAs were more likely than CAs to have extra-prostatic extension ($P = 0.026$) and less likely to have undergone a prior prostate biopsy ($P = 0.043$). Patients without CI

were more likely than patients with CI to have positive tumor margins ($P = 0.035$) and SV invasion ($P = 0.013$). This review of clinical pathology and patient population at Tulane hospital has been instrumental toward the project goals and characterization of chronic inflammation for this cohort.

- Major Task 2: Whole-exome sequencing of prostate tissue derived from tumor and chronic inflammation, and germline DNA. 50% complete. Samples are being prepared and shipped for whole-exome sequencing.
- Major Task 3: Perform genetic analyses characterizing somatic mutations in prostate tissue samples. 15% completed. In preparation for analyses, training in necessary techniques and applications is ongoing. Additional analyses are being conducted via TIMER: Tumor IMMune Estimation Resource (<https://cistrome.shinyapps.io/timer/>).
- Specific Aim 3: To compare and phylogenetically model intraprostatic genetic changes between prostate tissue with chronic inflammation and PCa.
 - Major Task 1: Compare and contrast genetic changes between prostate tissue with chronic inflammation and PCa. 0% completed.
 - Major Task 2: Confirm significant genetic alterations in an independent validation cohort. 20% completed. Clinical annotation and sample identification is ongoing in preparation for validation cohort; data, including presence of chronic inflammation, is being assembled for patients who have undergone radical prostatectomy at Tulane hospital.
- **What opportunities for training and professional development has the project provided?**
 - There have been many opportunities for training and professional development. The PI has continued to spend time in developing experience in clinical annotation of PCa. This includes direct experience in patient care through participation and observation during outpatient clinic appointments in both the Tulane Cancer Center and Urology clinics. Specifically, through direct interaction with both patients and physicians as well as evaluation of medical records, the PI is learning the clinical subtleties of treatment and management of PCa, current trends in PCa treatment and detection, and the diversity of the patient population, from newly diagnosed patients to end-of-life decision making. Additionally, the PI has had to opportunity to analyze and assess clinical genetic testing data with an emphasis on inflammatory genetic

markers. This clinical training has been invaluable for continued training as a translational researcher.

The PI also attended monthly Prostate Interest Group (PIG) meetings; these meetings consist of a multi-disciplinary group of basic scientists and clinicians focused on PCa research. These meetings have been essential for establishing intra- and inter-institutional collaborations, as well as an expert panel for assistance with the current project. The PI also attends a monthly tumor board focused on genitourinary malignancies. Aside for prostate specific meetings, the PI also regularly attends seminars hosted by the Louisiana Cancer Research Center (LCRC) and Louisiana State University Health Sciences Center Genetics Departmental Seminar series. Professional development has also included attendance and poster presentation at Genitourinary (GU) Cancers Symposium in Orlando, Florida.

The PI has had opportunities for professional development including teaching and supervisory roles. Specifically, the PI has given guest lectures for the Population Genetics course at Louisiana State University Health Sciences Center in the Department of Genetics. The PI has also given a lecture entitled “Prostate Cancer: A New Genetic Perspective” for Hayward Genetics Center grand rounds at Tulane University School of Medicine. In the lab, the PI has directly supervised and assisted with research projects for medical students, and graduate students. This supervision has included project design, guidance, technical assistance, meeting presentation, and ultimately publication.

▪ **How were the results disseminated to communities of interest?**

Nothing to Report.

▪ **What do you plan to do during the next reporting period to accomplish the goals?**

- Since this research is funded in part by the Tulane Prostate Cancer Research Fund, results will be presented at various outreach opportunities, fundraising, and educational events tailored for PCa patients. This includes presentations to monthly PCa support meetings, PSA screening events in conjunction with Tulane Urology and Tulane Cancer Center educational events. Additional opportunities for dissemination of this work include presentation of these results at interdepartmental seminars.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**
- A significant product of this research has been the creation of a very thorough and well annotated clinical history and mechanism for ongoing follow-up of African American PCa patients. This database contains and will contain a powerful translational dataset which combines clinical, pathological and genetic data. Specifically, as a disproportionately affected population which has been underrepresented in PCa genetic studies, the present study tools may give innovative genetic insights into both prostate inflammation and PCa in African American men. This type of genetic knowledge combined with detailed clinical annotation and long-term follow-up may empower patients and doctors to make personalized treatment decisions and ultimately improve treatment outcomes.

- **What was the impact on other disciplines?**
Nothing to report.

- **What was the impact on technology transfer?**
Nothing to report.

- **What was the impact on society beyond science and technology?**
Nothing to report.

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**
Nothing to report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
 - The first major delay encountered was due to the PI's pregnancy. She was on maternity leave from May- August and had to take intermittent sick time prior to maternity leave due to pregnancy complications. During this time work continued on this project; however, it was significantly delayed. Throughout maternity leave the PI continued to prepare for analyses and monitored continued progress toward sample sequencing.
The second major delay has been a prolonged contracting process with hospital facilities for the procurement and processing of tissue. Despite extensive communication between

institutional staff and hospital administrators, the contracting process has been ongoing since March. This delay was compounded due to the PI's maternity leave. Since returning, the PI has worked on resolving these issues and tissue has been prepared for acquisition and processing. To prevent further delays, the PI has proactively identified and selected tissue required for the validation component of this study; the established contract will be valid for the duration of this study.

The ongoing delay has been the turnover of laboratory and research staff. As new staff have been hired there have been delays affecting clinical annotation, patient identification and sample collection. Though resolved, this delay significantly impacted progression on the proposed study design; however, despite this disruption, the PI was able to complete additional training in other disciplines and perform additional analyses on available clinical genetic testing data.

- **Changes that had a significant impact on expenditures**

Nothing to report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

- **Significant changes in use or care of human subjects**

Nothing to report.

- **Significant changes in use or care of vertebrate animals.**

Nothing to report.

- **Significant changes in use of biohazards and/or select agents**

Nothing to report.

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**

- **Journal publications.** (See Appendix 2 for journal publication abstracts)

Chowdry, R. P., **E. Ledet**, L. Ranasinghe and A. O. Sartor (2016). "**MLL translocation in two castration-resistant prostate cancer patients.**" Can J Urol 23(5): 8483-8486. Case Report.

Pomerantz, M. M., S. Spisak, L. Jia, A. M. Cronin, I. Csabai, **E. Ledet**, A. O. Sartor, I. Rainville, E. P. O'Connor, Z. T. Herbert, Z. Szallasi, W. K. Oh, P. W. Kantoff, J. E. Garber, D. Schrag, A. S. Kibel and M. L. Freedman (2017). "**The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer.**" Cancer 123(18): 3532-3539.

Schiff, J. P., B. E. Lewis, **E. M. Ledet** and O. Sartor (2017). "**Prostate-specific Antigen Response and Eradication of Androgen Receptor Amplification with High-dose Testosterone in Prostate Cancer.**" Eur Urol 71(6): 997-998. Case Report.

Steinberger, A. E., P. Cotogno, **E. M. Ledet**, B. Lewis and O. Sartor (2017). "**Exceptional Duration of Radium-223 in Prostate Cancer With a BRCA2 Mutation.**" Clin Genitourin Cancer 15(1): e69-e71. Case Report.

- **Books or other non-periodical, one-time publications.**

Nothing to report.

- **Other publications, conference papers, and presentations.**

Guru Sonpavde, Rebecca J Nagy, A. Oliver Sartor, Gregory Russell Pond, Theodore Stewart Gourdin, Lakshminarayanan Nandagopal, **Elisa M. Ledet**, Neeraj Agarwal, Emma Carroll, Gurudatta Naik, Jue Wang, Mehmet Asim Bilen, Petros Grivas, Richard Burnham Lanman, AmirAli Talasaz, Michael B. Lilly. **Circulating tumor (ct)-DNA alterations in metastatic castration-resistant prostate cancer (mCRPC): association with outcomes and evolution with therapy.** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Lydia D. Chow, Patrick Cotogno, Emma M. Ernst, Charlotte Manogue, **Elisa M. Ledet**, Oliver Sartor. **Taste and prostate cancer: preliminary data on a novel patient reported outcome.** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Patrick Cotogno, **Elisa M. Ledet**, Joshua Schiff, Charlotte Manogue, Brian E. Lewis, Oliver Sartor. **AR Amplification Eradication with High Dose Testosterone (T) in heavily pre-treated mCRPC patient.** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Lahiru Ranasinghe, Patrick Cotogno, **Elisa M. Ledet**, Allie E. Steinberger, Allison H. Feibus, Kyle Degeyter, Bruce Bordlee, Oliver Sartor. **Liver Metastases in mCRPC Patients Post-Therapy with Abiraterone (Abi) and/or Abiraterone/Enzalutamide (Enza).** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Emma M. Ernst, **Elisa M. Ledet**, Joshua Schiff, Shuwen Lin, Cathryn E. Garvey, Oliver Sartor. **Characterization of cancer family history among PCa cancer patients.** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Joshua Schiff, **Elisa M. Ledet**, Emma M. Ernst, Cathryn E. Garvey, Patrick Cotogno, Oliver Sartor. **Family History, Race, and Prostate Cancer.** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Allison H. Feibus, Oliver Sartor, **Elisa M. Ledet**, Eric Shaw, Krishnarao Moparty, Raju Thomas, Jonathan L. Silberstein. **Utility of PCA3 and TMPRSS2:ERG Urinary Biomarkers to Predict Pathologic Outcomes in African American Men Undergoing Radical Prostatectomy.** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Shuwen Lin, **Elisa M. Ledet**, Joshua Schiff, Emma M. Ernst, Cathryn E. Garvey, Brian E. Lewis, Oliver Sartor. **Inherited pathologic mutations, and family history, in prostate cancer patients.** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Elisa M. Ledet, Oliver Sartor, Rayford Walter, Joan Bailey-Wilson, Diptasri Mandal. **Evidence of linkage in MSH6-associated region exclusive to high-risk African American families with prostate cancer.** Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

Elisa M. Ledet, Joshua Schiff, Patrick Cotogno, Charlotte Manogue, Emma M. Ernst,

Brian E. Lewis, Oliver Sartor. **Association of cfDNA Androgen Receptor Amplifications with BRAF Alterations in mCRPC**. Poster. 2017 Genitourinary Cancers Symposium. Orlando, FL.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

- A detailed database and clinical annotation has been assembled for the inflammation cohort at Tulane University Medical Center. Data collection for this database has been ongoing. This database includes detailed annotation of pathologic data, outside medical records, genetic testing, treatment history and ongoing follow-up. This database is supplemented with biospecimen collection, DNA, and RNA derived from the patient's radical prostatectomy; once sequenced, the resulting genetic data will be linked to this clinical annotation. This database will be a continuous resource for this study as well as other clinical studies evaluating early stage PCa. Ultimately, this database may be incorporated into a larger registry which will be used to facilitate collaboration and further translational research opportunities. Specifically, this database, which focuses on AAs, has been exceedingly useful in a number of studies beyond the present project. Utilizing the AA cohort, the PI has written and submitted two additional grants focused on prostate cancer disparity and underlying genetic risk factors.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Elisa Ledet, PhD
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Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	orcid.org/0000-0003-1230-3255
Nearest person month worked:	12
Contribution to Project:	Dr. Ledet has performed completed training associated with this award and continues progress on the proposed research plan.
Funding Support:	Institutional

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report.

- **What other organizations were involved as partners?**
 - **Organization Name:** Louisiana State University Health Sciences Center
 - **Location of Organization:** New Orleans, LA
 - **Partner's contribution to the project**
 - **Financial support:** None
 - **In-kind support:** Partner makes software available to PI
 - **Facilities:** PI uses partner facilities for project activities
 - **Collaboration:** Training in genetic epidemiological methods was provided by Diptasri Mandal, PhD.
 - **Personnel exchanges:** None
 - **Other:** None

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** Not applicable
- **QUAD CHARTS:** Not applicable

9. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

*Reminder: Pages shall be consecutively numbered throughout the report. **DO NOT** RENUMBER PAGES IN THE APPENDICES.*

Appendix 1. Tulane Inflammation cohort: Demographics.

	Demographic Data					P values			
	All Patients	Patients with CI		Patients <i>without</i> CI		Among All Patients		Among Patients with CI	Among Patients <i>without</i> CI
		AA	CA	AA	CA	AA vs. CA	CI vs. NO CI	AA vs. CA	AA vs. CA
N=	113	52	42	9	10				
Age:									
- Median (Range)	62 (41-75)	62 (50-71)	62 (50-75)	62 (50-68)	57 (41-67)	N/A	N/A	N/A	N/A
BMI									
- Median (Range)	28.79 (14.27-46.75)	25.96 (14.27-41.50)	27.90 (21.62-41.41)	29.78 (23.10-36.29)	29.83 (22.90-46.75)	0.589 ¹	0.116 ¹	N/A	N/A
Family History of Prostate Cancer:									
- No	69 (61.1%)	33 (63.5%)	24 (57.1%)	6 (66.7%)	6 (60.0%)	0.559 ²	1.000 ³	0.641 ²	1.000 ³
- Yes	28 (24.8%)	12 (23.1%)	11 (26.2%)	2 (22.2%)	3 (30.0%)				
- Unknown	16 (14.2%)	7 (13.5%)	7 (16.7%)	1 (11.1%)	1 (10.0%)				
Treatment:									
- RARP	105 (92.9%)	50 (96.2%)	36 (85.7%)	9 (100.0%)	10 (100.0%)	N/A	N/A	N/A	N/A
- AS, RARP	8 (7.1%)	2 (3.8%)	6 (14.3%)						

RARP= Robot assisted radical prostatectomy; AS= Active surveillance ; ¹ P value from two-way ANOVA test; ² P value from Pearson chi square; ³ P values from Fisher's exact test

Appendix 2. Journal Publication abstracts.

Chowdry, R. P., **E. Ledet**, L. Ranasinghe and A. O. Sartor (2016). "**MLL translocation in two castration-resistant prostate cancer patients.**" *Can J Urol* 23(5): 8483-8486. Case Report.

The mixed-lineage leukemia (MLL) protein acts as a histone methyltransferase regulating multiple genetic elements. Rearrangements of the MLL gene result in expression of MLL-fusion proteins that occur in some acute leukemias and are associated with poor prognosis. The MLL protein complex has been shown to interact with the androgen receptor via the MLL-menin subunit, thus promoting gene activation. The presence of MLL translocation has not been previously reported in patients with castrate resistant prostate cancer (CRPC). We describe two cases of metastatic CRPC with a translocation in the MLL gene detected by a specific fluorescent in situ hybridization (FISH) assay. Both patients had an aggressive course and succumbed to the illness.

Pomerantz, M. M., S. Spisak, L. Jia, A. M. Cronin, I. Csabai, **E. Ledet**, A. O. Sartor, I. Rainville, E. P. O'Connor, Z. T. Herbert, Z. Szallasi, W. K. Oh, P. W. Kantoff, J. E. Garber, D. Schrag, A. S. Kibel and M. L. Freedman (2017). "**The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer.**" *Cancer* 123(18): 3532-3539.

BACKGROUND: Breast cancer 2 (BRCA2)-associated breast and ovarian cancers are sensitive to platinum-based chemotherapy. It is unknown whether BRCA2-associated prostate cancer responds favorably to such treatment.

METHODS: A retrospective analysis of a single-institution cohort of men with castration-resistant, metastatic prostate cancer was performed to determine the association between carrier status of pathogenic BRCA2 germline variants and prostate-specific antigen response to carboplatin-based chemotherapy. From 2001 through 2015, 8081 adult men with prostate cancer who had a consultation and/or underwent treatment at Dana-Farber Cancer Institute provided blood samples and consented to analyses of biologic material and clinical records. A subgroup of 141 men received at least 2 doses of carboplatin and docetaxel for castration-resistant disease (94% were also taxane refractory). These patients were categorized according to the absence or presence of pathogenic germline mutations in BRCA2 based on DNA sequencing from whole blood. The primary outcome was the response rate to carboplatin/docetaxel chemotherapy, defined according to a decline in prostate-specific antigen that exceeded 50% within 12 weeks of initiating this regimen. Associations between BRCA2 mutation status and response to carboplatin-based chemotherapy were tested using the Fisher exact test, with a 2-sided P value < .05 as the threshold for significance.

RESULTS: Pathogenic germline BRCA2 variants were observed in 8 of 141 men (5.7%; 95% confidence interval, 2.5%-10.9%). Six of 8 BRCA2 carriers (75%) experienced prostate-specific antigen declines >50% within 12 weeks, compared with 23 of 133 noncarriers (17%; absolute difference, 58%; 95% confidence interval, 27%-88%; P < .001). Prostate cancer cell lines functionally corroborated these clinical findings.

CONCLUSIONS: BRCA2-associated, castration-resistant prostate cancer is associated with a higher likelihood of response to carboplatin-based chemotherapy than non-BRCA2-associated prostate cancer. *Cancer* 2017;123:3532-9. © 2017 American Cancer Society.

Schiff, J. P., B. E. Lewis, **E. M. Ledet** and O. Sartor (2017). "**Prostate-specific Antigen Response and Eradication of Androgen Receptor Amplification with High-dose Testosterone in Prostate Cancer.**" Eur Urol 71(6): 997-998. Case Report.

Steinberger, A. E., P. Cotogno, **E. M. Ledet**, B. Lewis and O. Sartor (2017). "**Exceptional Duration of Radium-223 in Prostate Cancer With a BRCA2 Mutation.**" Clin Genitourin Cancer 15(1): e69-e71. Case Report.

Clinical Practice Points

- It is now recognized that patients with prostate cancer have a higher rate of DNA repair gene mutations than previously appreciated.
- The prevalence of germline alterations in DNA repair genes may be as high as 11.8% in patients with metastatic prostate cancer.
- Several targeted agents for DNA repair defects (poly ADP ribose polymerase inhibitors and platinum) have shown increased sensitivity in the setting of biallelic breast cancer susceptibility gene 2 (BRCA2) loss.
- The mechanism of action of Radium-223, a bone-targeted radiopharmaceutical, raises the possibility of clinical exploitation among patients with a BRCA2 mutation.
- We hypothesize that the extraordinary duration of disease control with Radium-223 described herein is owing to the presence of a unique sensitivity in patients with a BRCA2 mutation.